

Available online on 15.10.2018 at <http://jddtonline.info>**Journal of Drug Delivery and Therapeutics**

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Review Article

**CHEMICAL PENETRATION ENHANCERS FOR TRANSDERMAL DRUG DELIVERY SYSTEM****Kapoor Anupriya<sup>\*</sup>, Mishra Shashi Kiran, Verma Dharmesh Kumar, Pandey Prashant**

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**ABSTRACT**

In present scenario more than 70% of the drugs that are taken by oral route are found to be less effective as desired, to overcome this constraint Transdermal drug delivery system has emerged as an innovative area of research, this system helps in delivering the drugs and macromolecules through skin into systemic circulation. At present, the worldwide market of Transdermal patch has reached 2 billion pounds. Many drugs like Estrogen, Progesterone, Nitroglycerine, Clonidine etc. are fabricated in form of Transdermal patches due to its ability to deliver the drug in non-invasive manner and also to overcome the problems associated with oral route. Although the Transdermal patches deliver the drug at predetermined rate<sup>1</sup>, the partitioning of drug from the system to the skin and then penetration through different layers of skin can be altered by adding penetration enhancers that can be physical or chemical in nature. This article deals with the role of different chemicals that can be used as penetration enhancer.

**Keywords:** Penetration enhancer, Layer of skin, Fatty alcohol and glycol**Article Info:** Received 02 Sep, 2018; Review Completed 30 Sep 2018; Accepted 02 Oct 2018; Available online 15 Oct 2018**Cite this article as:**Kapoor A, Mishra SK, Verma DK, Pandey P, Chemical penetration enhancers for transdermal drug delivery system, Journal of Drug Delivery and Therapeutics. 2018; 8(5-s):62-66 DOI: <http://dx.doi.org/10.22270/jddt.v8i5-s.1952>**\*Address for Correspondence:**

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**INTRODUCTION****Drug delivery through skin**

Skin being the largest organ of the body, has total area of about 20 square feet. it protects us from microbes and other ailments, helps to regulate body temperature, and permits the sensations of touch, heat, and cold<sup>2</sup>.

**Layers of skin****Non-viable epidermis (stratum corneum)**

It is the outer most layer of skin, being an actual physical barrier to most substance that come in contact with the skin, it acts as barrier to the entry of foreign substances. Stratum corneum is 10 to 20 cell layer thick over most of the body. The composition of Stratum corneum comprises of lipids like phospholipids, cholesterol, neutral lipids etc.

The other component being proteins, the major fraction of which is Keratin.

**Viable epidermis**

This layer of the skin is found between the stratum corneum and the dermis, the thickness ranges from 50- 100 µm. The structure of the cells in the viable epidermis is physiochemical similar to other living tissues. The water content is about 90%.

**Dermis**

Just beneath the viable epidermis is the dermis. It is a structural fibrin and very few cells are like it can be found histologically in normal tissue. Dermis thickness range from 2000 to 3000 µm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amorphous ground substance.

### Subcutaneous connective tissue

The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretory pores of the sweat gland and cutaneous nerves. Most investigators consider drug permeating through the skin enter the circulatory system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug.

### Sites of drug penetration through skin<sup>3</sup>

Intercellular route: it is the most common pathway through which the drugs cross through the skin, the drugs pass through the small gaps between the cells of skin

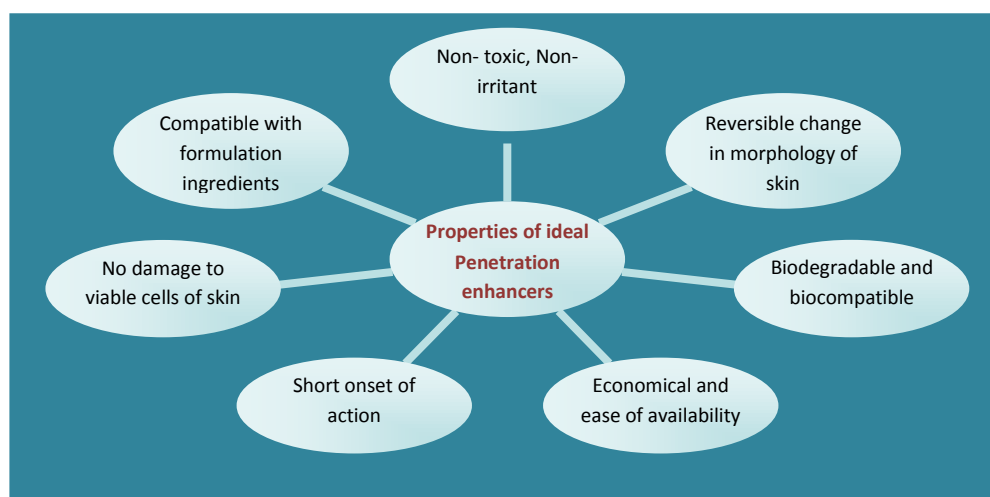
Transcellular route: drugs pass the skin through the keratinocyte cells

Follicular route: drugs pass through sweat gland, hair follicles and sebaceous glands

### Penetration enhancers:

Chemical penetration enhancers are proven to increase the transport of drug across the skin layers. They show their effect by different mechanisms that depend on the chemical nature of penetration enhancer, the mechanism may include disruption of lipid bilayers of stratum corneum or extraction of intercellular protein; Keratin and thus modify the penetration ability of drugs<sup>4</sup> or may improve the partitioning of drug due to solvent action. Chemical penetration enhancers temporarily diminish the barrier nature of skin and known to accelerate or enhance drug flux.

### Properties of chemical penetration enhancers<sup>5</sup>



### Classes of penetration enhancers

- Fatty acids
- Fatty alcohols
- Terpenes
- Sulfoxides
- Anionic surfactants
- Cationic surfactants
- Non-ionic surfactants
- Zwitter ion surfactants
- Ureas

**Fatty acids** like oleic acid, linolenic acid, palmitoleic acid etc. Are included in GRAS (generally regarded as safe) list and are found to be effective penetration enhancers that could be incorporated in transdermal patches, the acid interact with the lipoidal components of stratum corneum and may modify the extent of partitioning of drug from the patch and its penetration into skin. The efficacy of an acid

as enhancer depends upon its structure, length of alkyl chain and extent of unsaturation<sup>6</sup>. Fatty acids with short chain are found to be more effective in disrupting the lipoidal component of stratum corneum when they are incorporated in nonpolar solvents; on the contrary long chain fatty acids are more effective in polar solvents. In case of saturated fatty acid a polar head with C10 to C12 helps in potentiating the efficacy of enhancer where as in case of unsaturated fatty acid a polar head with C18 gives optimum effect.

**Fatty alcohol and glycols** solvents like ethanol, propylene glycol, diethylene glycol, manitol etc. are known to increase the penetration of several compounds. The mechanism by which these solvents act is based on the extraction of lipids from cells of stratum corneum<sup>7</sup> the extraction of lipids result in formation of pores thus increasing the cutaneous hydration and solubility of solutes.

**Terpenes** natural terpenes like Anithole, Camphor, Borneol, Eugenol etc. are known to exhibit penetration enhancing ability as exhibited by several researches, the

exact mechanism by which terpenes act is not clear but experimentally it has been demonstrated that they act by several ways like helping the drug molecule to diffuse through stratum corneum by extracting intercellular lipids, they may also extract lipids of stratum corneum and breaking of hydrogen bond. They may also act by increasing the lipid fluidity and improving the partitioning of drug. Camphor shows its action by disrupting the regular organization of stratum corneum<sup>8,9,10</sup>.

**Sulfoxides:** sulfoxides and similar molecules like DMSO (dimethyl sulfoxide), DMF (dimethyl formamide) etc. are known to demonstrate penetration enhancing power. DMSO is a commonly explored penetration enhancer, it is an aprotic solvent that has been used to prepare topical formulations for several drugs like antibiotics, steroids, narcotics etc<sup>11</sup>. DMSO causes structural changes in stratum corneum layer, it interacts with  $\alpha$ -keratin proteins and convert them to  $\beta$ -sheet conformation, these conformational alterations in skin layer as well as DMSO induced variations in lipid composition of skin are responsible for its penetration enhancing power across the skin<sup>12</sup>. Although both DMSO and DMF have good penetration enhancement power but they cause irreversible cell membrane damage at higher concentrations above 60%<sup>13</sup>.

**Anionic surfactants:** sodium lauryl sulphate is an example of anionic surfactant that has found a wide application as penetration enhancer. Anionic surfactants are more efficacious than non-ionic or cationic surfactants, it is observed that anionic surfactants interact with keratin and lipid of stratum corneum cells, it alters the skin permeability by uncoiling the keratin filament, by increasing the fluidity of epidermal cells and also by increasing the hydration of skin due to hydrophobic interaction of alkyl chain with skin structure.<sup>14, 15</sup>

**Cationic surfactants:** cationic surfactants show interaction with the keratin fibrils of the cornified cells and result in disruption of cellular-lipid matrix. The cationic surfactants may also show interaction with anionic components of the stratum corneum and thus cause a change in electronic property at the site, and thus stimulate the passage of the anionic drug across the skin layer<sup>16</sup>.

**Non-ionic surfactants:** Non-ionic surfactants demonstrate their penetration enhancer ability by causing the fluidization of stratum corneum, the surfactant initially penetrates into the intercellular spaces of stratum corneum due to which fluidity is increased because of solubilisation and extraction of lipid. The surfactant may also interact with the keratin filaments and result in disruption of cells of stratum corneum<sup>17</sup>.

**Zwitterionic surfactants:** dodecylbetaine, hexadecylbetaine, hexadecylsulfobetaine, N, N-dimethyl-N-dodecyl amine oxide, dodecyltrimethylammonium bromide etc. are few zwitterionic surfactants that have experimentally demonstrated their ability to act as penetration enhancer; they act by solubilization of lipids of stratum corneum<sup>18</sup>.

**Ureas:** urea and its derivatives have been used in topical and transdermal preparations due to its moisturising,

keratolytic and penetration enhancing applications<sup>19</sup>. Urea causes the hydration of stratum corneum by the formation of hydrophilic channels within the barrier layer of skin. They are also known to cause disruption of lipid matrix of stratum corneum thereby increasing the penetration of molecules across the skin. A cyclic structure in urea derivatives makes them biodegradable and non-toxic which makes them suitable for their role as penetration enhancers<sup>20</sup>.

## Research in field of Transdermal patches

1. Formulation of patches of Repaglinide to provide sustain release and to improve the bioavailability of drug<sup>21</sup>.
2. Formulation and evaluation of transdermal patches of Propranolol hydrochloride in order to overcome its first pass metabolism and to demonstrate the effect of Eugenol as permeation enhancer<sup>22</sup>.
3. Designing of patches of Diclofenac sodium using cellulose acetate phthalate polymer and to study the effect of different penetration enhancers like isopropylmyristate, Tween 80, oleic acid, linoleic acid<sup>23</sup>.
4. Development of reservoir type transdermal patch of iso-sorbide nitrate for sustain effect<sup>24</sup>.
5. Formulation and evaluation of patch for Donepezil with aim to improve its patient compliance and therapeutic efficacy<sup>25</sup>.
6. Formulation of Indomethacin Transdermal patches and to evaluate the effect of Patchouli oil as penetration enhancer<sup>26</sup>.
7. Formulation of Transdermal patches of Torasemide to avoid first pass metabolism and to avoid irritation due to intra-venous therapy of drug<sup>27</sup>.
8. Preparation of patches of Risperidone to avoid the oral side effects of drug in treatment of schizophrenia<sup>28</sup>.
9. Formulation of monolithic Transdermal patches of Salbutamol sulphate and to evaluate the effect of penetration enhancer<sup>29</sup>.
10. Formulation of self adhesive matrix type Transdermal patch of Ondansetron<sup>30</sup>.
11. Designing of Transdermal patches for combination of Diclofenac and Teriflunomide for treatment of rheumatoid arthritis<sup>31</sup>.
12. Formulation of matrix type patches of Olanzapine and to observe the effect of eucalyptus oil as penetration enhancer<sup>32</sup>.
13. Formulation of Transdermal patch of combination of Salbutamol and Ketotifen fumarate<sup>33</sup>.
14. Formulation of Transdermal patches of Flubiprofen and evaluation of milk thistle oil and olive oil as penetration enhancer<sup>34</sup>.
15. Formulation of matrix type Transdermal patch of Zaleplon<sup>35</sup>.

16. Formulation of Transdermal patch of Papaveirine hydrochloride by solvent casting method<sup>36</sup>.
17. Formulation of Transdermal patch for Aceclofenac for rheumatoid arthritis<sup>37</sup>.
18. Formulation of Transdermal patches of Carvedilol with novel polymers like HPMCK100, Eudragit RL100, HPMC E5 and PVA<sup>38</sup>.
19. Reservoir type Transdermal patches of Hydralzine hydrochloride and to study the effect of penetration enhancers<sup>39</sup>.
20. Development of Transdermal patch of Lisinopril dehydrates to overcome its poor oral bioavailability<sup>40</sup>.
21. Formulation of Transdermal patch of Lamotrigine using terpenes as natural penetration enhancer<sup>41</sup>.
22. Development of Transdermal patch of Nicardipine hydrochloride and to evaluate the effect of eugenol and DMSO as penetration enhancer<sup>42</sup>.
23. Designing of Transdermal patch of Atorvastatin<sup>43</sup>.
24. Formulation of Transdermal patches of Curcumin for wound healing effect<sup>44</sup>.
25. Formulation of Simvastatin nanoparticles loaded transdermal patches<sup>45</sup>.
26. Formulation and evaluation of matrix type patch of Ondansetron<sup>46</sup>.
27. Formulation of matrix type patch for Rivastigmine tartrate<sup>47</sup>.

## CONCLUSION

Since Transdermal drug delivery system is emerging as a field of interest in order to deliver the drug to the patient with compliance, the use of penetration enhancers in patches have led to a significant increase in drug permeation through skin however focus should be imparted on problems like skin irritation and allergy caused by these chemicals when they are used in higher concentrations.

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